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Renal risk and renoprotection among ethnic groups with type 2 diabetic nephropathy: A *post hoc* analysis of RENAAL

D de Zeeuw[1], D Ramjit[2], Z Zhang[2], AB Ribeiro[3], K Kurokawa[4], JP Lash[5], J Chan[6], G Remuzzi[7], BM Brenner[8] and S Shahinfar[2]

[1]*Department of Clinical Pharmacology, Groningen University Medical Center, Groningen, The Netherlands;* [2]*Merck Research Laboratories, Merck & Co. Inc., Whitehouse Station, New Jersey, USA;* [3]*Nephrology Division-UNIFESP – EPM, Hospital Do Rim E Hipertensão-Fundação Oswaldo Ramos, Sau Paulo, Brazil;* [4]*Dean's Office, Tokai University School of Medicine, Kanagawa, Japan;* [5]*Section of Nephrology, Department of Medicine, University of Illinois at Chicago, Chicago, Illinois, USA;* [6]*Department of Medicine and Therapeutics, The Chinese University of Hong Kong, The Prince of Wales Hospital, Hong Kong, China;* [7]*Mario Negri Institute for Pharmacological Research, Bergamo, Italy and* [8]*Renal Division, Department of Medicine, Brigham and Women's Hospital and Harvard School of Medicine, Boston, Massachusetts, USA*

Type 2 diabetes is becoming the leading cause of end-stage renal disease (ESRD) worldwide. Prevalence of ESRD and the antihypertensive response to renin–angiotensin system intervention are suggested to vary among different ethnicities. The Reduction in Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study, which included different ethnic groups, demonstrated a renoprotective effect of losartan. A *post hoc* analysis from RENAAL was performed where we examined in each ethnic group the ESRD risk, identified independent predictors for ESRD, effect of degree of baseline albuminuria, effect of 6-month antiproteinuric response to therapy on ESRD, and renoprotective effect of losartan assessed by albuminuria reduction and ESRD. Baseline albuminuria was the strongest predictor for ESRD in every ethnic group. Albuminuria reduction was associated with reduced risk of ESRD while losartan reduced albuminuria in every ethnic group. When accounting for independent predictors of ESRD, losartan exhibited renoprotection in all ethnic groups. In this type 2 diabetic population with nephropathy, baseline albuminuria is the predominant risk parameter for ESRD; early antiproteinuric effect of losartan predicts long-term renoprotection; and losartan appears to be renoprotective in all ethnic groups. Since the RENAAL study was not powered to determine ethnic responses, these results underline the need for prospective trials where the aim is renal protection among different ethnic groups.

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Correspondence: *D de Zeeuw, Department of Clinical Pharmacology, University Medical Center Groningen, Ant Deusinglaan 1, Groningen 9713 AV, The Netherlands. E-mail: d.de.zeeuw@med.umcg.nl*

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Worldwide, diabetes mellitus is one of the most common diseases[1] and has become a major cause of end-stage renal disease (ESRD).[2,3] Ethnic differences in ESRD have been widely reported. Earlier and more recent population-based studies consistently have shown that in diabetic and non-diabetic patients, Black, and in some reports, Asian patients, experience higher rates of ESRD, whereas White patients experience lower rates.[4–8] Higher incidences of ESRD have been reported in Hispanic patients with or without diabetes, relative to White patients.[2,7–9]

Given the fact that nephropathy occurs in approximately 10–40% of diabetic patients,[10] early identification of patients with type 2 diabetes who are at increased risk for renal disease and early initiation of treatment to slow progression to ESRD is of great importance for all ethnic groups. Proteinuria, azotemia, anemia, hyperglycemia, hypertension, and hyperlipidemia have been shown to be risk factors for renal and cardiovascular outcomes in type 2 diabetes.[11–15] However, whether these risk factors for outcome play the same predictive role among different ethnicities is not known. Proteinuria is one of the most widely recognized risk factors for renal disease progression.[16–18] Proteinuria has been studied in different ethnic groups; however, the findings have been variable with respect to the prevalence and severity of proteinuria among those groups.[19–25]

Several large clinical trials have shown that intervention using antihypertensives that block the renin—angiotensin system (RAS) are beneficial in reducing the incidence of cardiovascular and renal outcomes in diabetic patients.[26–29] Whether such a treatment strategy is equally beneficial to

diabetic patients across different ethnicities is not known. In fact, it has been suggested that the *antihypertensive response* to RAS blockade is less effective than other therapeutic classes in Black patients relative to non-black patients.[30,31] However, limited data are available on the effect of RAS blockade on cardiovascular and renal outcomes comparing different ethnic groups simultaneously and prospectively.

The Reduction in Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study was the first to demonstrate that RAS blockade with losartan is effective in reducing the incidence and delaying the onset of ESRD in patients with type 2 diabetes and nephropathy.[29] Additionally, baseline proteinuria has been shown to be the leading risk predictor for renal outcomes including ESRD in this population.[12] Furthermore, angiotensin II antagonist (AIIA)-induced reduction in proteinuria appears to be a good predictor for long-term renal and cardiovascular protection.[11,12] The RENAAL study, to our knowledge, is the only study that has recruited type 2 diabetic patients with renal disease worldwide, including relatively large numbers of White, Black, Hispanic, and Asian patients. ESRD was observed in each ethnic group, which has allowed us to explore risk of renal outcomes and the renoprotective effect of losartan therapy across those groups. We also investigated if similar renal risk factors are present in each ethnic group. Moreover, in each ethnic group, we examined whether the reduction in albuminuria affords the same renal protection, and whether RAS intervention with losartan leads to the same risk reduction in ESRD. In the present report, we focus on the irreversible renal outcome of ESRD, as this outcome was ascertained in all patients randomized to the study, and represents the final stage of renal disease progression, and the ultimate therapeutic target for renal protection.

RESULTS

Baseline risk factors as predictors of ESRD by ethnic group

Table 1 summarizes baseline demographic parameters for the RENAAL population stratified by ethnic group. We observed expected differences in weight among the ethnic groups, with the Asian patients having the lowest weight (64 kg) and the Black and White patients having the highest weights (92 and 88 kg, respectively) in the study.

Hemoglobin was lowest in the Black patients and highest in White patients (12.0 and 12.8 mg/dl, respectively). Serum creatinine, systolic blood pressure (BP), and diastolic BP were comparable among all ethnic groups. Notable differences were observed among the groups in baseline albuminuria, which was considerably higher in Hispanic and Asian patients (2.40 and 2.01 g/g, respectively) and lowest in Black patients (1.22 g/g). Figure 1 clearly illustrates that the distribution of baseline albuminuria levels varied among ethnic groups.

The risk for ESRD among ethnic groups is depicted in Figure 2. The Hispanic and Asian populations show a somewhat higher risk for ESRD than the Black and White populations. A multivariate analysis was performed to determine the relative impact of selected baseline risk factors on ESRD in the different ethnic groups. Table 2 shows that of the selected baseline risk factors included in the multivariate model, baseline albuminuria was the strongest independent predictor of ESRD in all ethnic groups: Asian (hazard ratio (HR) = 1.33), Black (HR = 1.81), Hispanic (HR = 1.46), and White (HR = 1.62).

The distribution of baseline albuminuria was variable among ethnic groups. Despite these differences, we observed that a similar degree of albuminuria predicted a similar degree of risk for ESRD across ethnic groups. As shown in Figure 3, higher levels of baseline albuminuria were associated with progressively increased risk of ESRD (controlled for baseline risk factors) for all ethnic groups.

Six-month change in albuminuria as a predictor for ESRD by ethnic group

Data from the RENAAL study suggest that albuminuria reduction observed in the first 6 months of treatment is predictive of the efficacy of treatment on renal outcomes.[12] The relationship between different degrees of month-6 albuminuria reduction and the risk for ESRD is depicted in Figure 4 for each ethnic group. Similar to the overall population,[12] albuminuria reduction was associated with reduced risk of ESRD (controlled for baseline and changes in month-6 risk factors) in all ethnic groups.

Renoprotective effect of losartan by ethnic group

Losartan-reduced albuminuria in the overall population by 34%.[29] Figure 5 illustrates mean change in albuminuria during the course of the study in each ethnic group. Over time, mean reductions in albuminuria were observed in the placebo groups of each ethnic group, especially after the first 12 months of the study. The albuminuria reductions with placebo most likely were influenced by premature discontinuation of study drug, ESRD or death. Progressive reductions in albuminuria with losartan were observed as early as month-3 in all ethnic groups (Figure 5).

The renoprotective effect of losartan in the overall RENAAL population was characterized by a 28% risk reduction in ESRD when comparing losartan to placebo, with both treatment groups on a background of conventional antihypertensive treatment.[29] Figure 6 illustrates the losartan treatment effect for ESRD by ethnic group. The renoprotective effect of losartan based on the pre-specified analysis (Figure 6, solid lines), was most favorable in the White and Asian groups followed by the Black group; while a neutral treatment effect for ESRD was observed in the Hispanic ethnic group. However, given the importance of baseline albuminuria and other variables as independent predictors of risk, the treatment effects for ESRD for each ethnicity were controlled for their respective baseline risk predictors identified in the multivariate analysis (Table 2). The renoprotective response of losartan when accounting for these risk factors (Figure 6, dashed lines) was improved in all

Table 1 | Patient demographic and other baseline characteristics by ethnic group

Variable	Statistics	Asian	Black	Hispanic	White
Gender	*N*	252	230	277	735
Female	*n* (%)	81 (32.1)	94 (40.9)	128 (46.2)	243 (33.1)
Male	*n* (%)	171 (67.9)	136 (59.1)	149 (53.8)	492 (66.9)
Smoking	*N*	249	230	277	734
Yes	*n* (%)	52 (20.9)	46 (20.0)	43 (15.5)	130 (17.7)
Age (years)	*N*	252	230	277	735
	Mean (s.d.)	59.6 (7.3)	59.1 (7.8)	59.0 (7.5)	61.2 (7.2)
	Range	36.0–72.0	31.0–73.0	40.0–74.0	34.0–73.0
BMI (kg/m^2)	*N*	244	224	269	722
	Mean (s.d.)	25.0 (4.5)	32.0 (6.2)	28.3 (6.6)	31.0 (5.7)
	Range	15.6–50.5	19.6–56.3	18.0–59.6	16.1–53.9
Weight (kg)	*N*	252	230	277	735
	Mean (s.d.)	64.3 (13.1)	92.2 (19.1)	73.6 (19.6)	88.2 (18.7)
	Range	32.0–132.2	48.1–159.7	40.0–161.0	48.1–158.8
DBP (mmHg)	*N*	252	230	277	735
	Mean (s.d.)	81.5 (10.8)	82.7 (11.1)	82.4 (9.4)	82.5 (10.5)
	Range	37.0–111.0	55.0–120.0	53.0–108.0	43.0–117.0
SBP (mmHg)	*N*	252	230	277	735
	Mean (s.d.)	151.8 (19.3)	149.9 (18.6)	150.3 (19.7)	154.5 (19.3)
	Range	105.0–199.0	107.0–199.0	97.0–200.0	100.0–226.0
HBA1c (%)	*N*	249	226	277	726
	Mean (s.d.)	8.1 (1.5)	8.9 (1.7)	8.8 (1.9)	8.3 (1.5)
	Range	4.8–13.2	5.0–13.9	5.1–17.5	4.8–13.4
Hemoglobin (gm/dl)	*N*	239	226	273	711
	Mean (s.d.)	12.2 (2.0)	12.0 (1.7)	12.3 (1.9)	12.8 (1.7)
	Range	7.9–17.1	7.8–15.9	6.8–17.4	8.4–18.0
Serum creatinine (mg/dl)	*N*	252	230	277	735
	Mean (s.d.)	1.9 (0.4)	1.8 (0.5)	1.9 (0.5)	1.9 (0.5)
	Range	1.0–3.1	1.1–3.3	0.9–3.4	1.0–3.6
Cholesterol (mg/dl)	*N*	252	228	276	723
	Mean (s.d.)	228.0 (51.2)	222.7 (53.8)	237.6 (56.1)	225.4 (56.5)
	Range	126.0–426.0	120.0–402.0	114.0–495.0	97.0–480.0
Albuminuria (g/g)	*N*	252	230	277	735
	Mean (s.d.)	2.01 (1.72)	1.22 (1.19)	2.40 (2.13)	1.69 (1.53)
	(GM)	(1.35)	(0.78)	(1.62)	(1.10)
	Range	0.03–10.15	0.03–7.70	0.09–12.21	0.03–9.95
Proteinuria[a] (g/day)	*N*	42	144	193	330
	Mean (s.d.)	3.12 (2.94)	2.63 (2.50)	4.30 (4.01)	3.39 (3.54)
	(GM)	(2.02)	(1.75)	(2.85)	(2.15)
	Range	0.11–13.49	0.19–11.97	0.37–23.25	0.03–23.82

BMI: body mass index; DBP: diastolic blood pressure; GM: Geometric mean; SBP: systolic blood pressure.
The analysis was based on observed data without imputation on missing values.
[a]Subgroup of patients in whom 24 h urine was collected (see Materials and Methods section).

ethnic groups, especially in Hispanic patients, where the HR fell from 1.02 (95% confidence interval (CI): 0.66, 1.59) to 0.81 (95% CI: 0.52, 1.27).

In each ethnic group, the potential impact of BP changes on the treatment effect for ESRD was examined. Table 3 presents treatment effect of losartan based on the pre-specified analysis (depicted by the solid lines in Figure 6) and after adjustment for systolic and diastolic BP as a time-varying covariate (post-randomization). Treated BP does not appear to have a notable impact on the treatment effect for ESRD, as the HRs for the ethnic groups after adjusting for time-varying BP remain stable or slightly increased (Table 3).

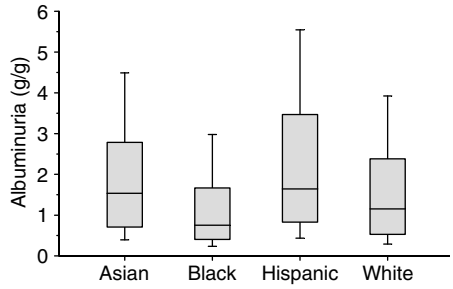
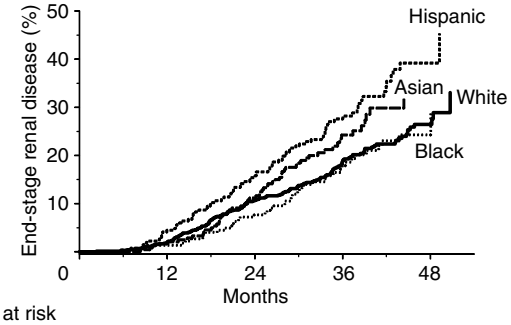


Figure 1 | Distribution of baseline albuminuria stratified by ethnic group. Each box represents albuminuria levels by quantiles. The lowest and highest boundaries below and above each box represent the 10th and 90th% quantiles, respectively. The bottom, middle, and top of each box represent the 25th, 50th, and 75th% quantiles, respectively.



No. at risk

Asian	252	237	212	94	12
Black	230	221	198	113	16
Hispanic	277	253	209	122	16
White	735	700	602	384	66

Figure 2 | Event rate of ESRD stratified by ethnic group. The cumulative proportion (%) of patients in each ethnic group that reached ESRD was estimated using the Kaplan–Meier procedure.

Table 2 | Multivariate analysis for the effect of baseline risk markers on ESRD (ordered by χ^2 statistics)

Ethnic group	Independent base risk factors[a]	HR (95% CI)	χ^2	*P*-value
Asian	Albuminuria	1.33 (1.19, 1.48)	27.0	0.000
	Hemoglobin	0.70 (0.60, 0.82)	20.6	0.000
	Age	0.60 (0.41, 0.87)	7.1	0.008
Black	Albuminuria	1.81 (1.53, 2.14)	48.4	0.000
	Serum creatinine	8.03 (4.25, 15.17)	41.1	0.000
Hispanic	Albuminuria	1.46 (1.35, 1.58)	94.0	0.000
	Serum creatinine	3.15 (2.06, 4.81)	28.1	0.000
White	Albuminuria	1.62 (1.49, 1.75)	134.0	0.000
	Serum creatinine	5.02 (3.70, 6.82)	106.8	0.000
	Male vs. Female	0.52 (0.37, 0.73)	14.1	0.000

CI: confidence interval; ESRD: end-stage renal disease; HR: hazard ratio.
All patients were included with missing covariates imputed.
[a]Selected from baseline covariates listed in the Statistical analysis section.

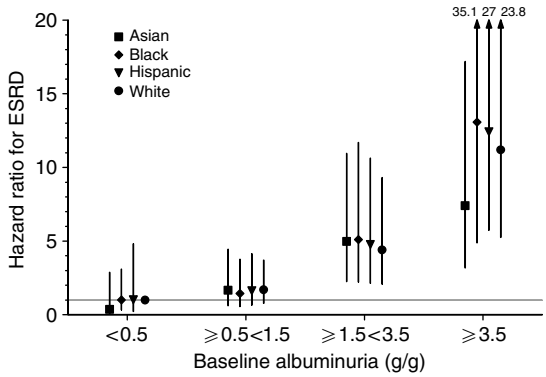


Figure 3 | Risk for ESRD versus baseline albuminuria stratified by ethnic group. The HR with 95% CI is referenced at albuminuria <0.5 g/g in White patients. HR is controlled for all baseline risk markers summarized in the Statistical analysis section.

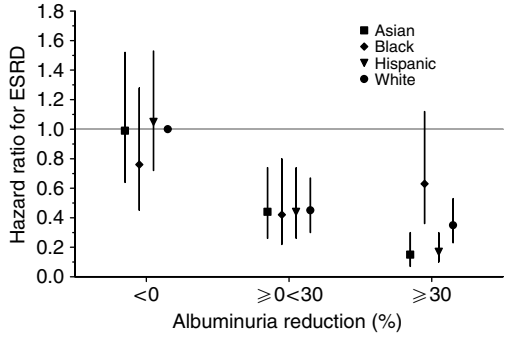


Figure 4 | Risk for ESRD versus albuminuria reduction stratified by ethnic group. The HR with 95% CI is calculated relative to 0% change in albuminuria. The HR is controlled for all risk markers at baseline and month-6 changes, summarized in the Statistical analysis section.

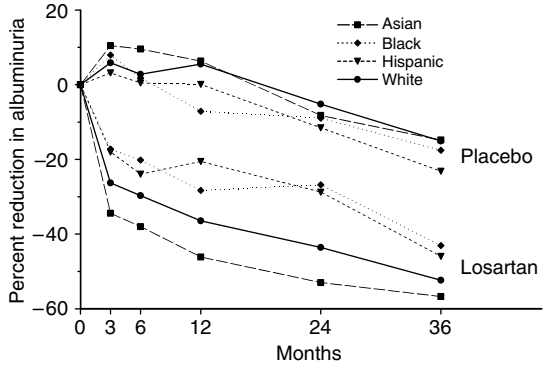


Figure 5 | Mean percent change from baseline in albuminuria over time stratified by ethnic group.

DISCUSSION

For all ethnic groups (i.e. Asian, Black, Hispanic, and White), the most important, independent, baseline factor that determines renal risk for ESRD is albuminuria (higher albuminuria associated with greater renal risk), followed by either baseline serum creatinine or hemoglobin. In this study, the risk for ESRD appears to be higher in the Hispanic and Asian ethnic groups. We found that treatment induced

change in albuminuria at month-6 predicts the longer-term renoprotective effect in a similar manner for Black, Asian, Hispanic, and White patients. Controlling for differences in baseline risk profile for each ethnic group, our results indicate that losartan affords renoprotection with regard to ESRD and reduction in albuminuria, irrespective of ethnicity.

Although many large clinical studies examining the effect of treatment on renal outcome were multinational, all of them were conducted in a limited number of geographical regions.[19,28,32–35] Unlike these studies, RENAAL was not only carried out in multiple regions of the world, which included North and South America, Europe, and Asia (southeast region and Japan); but also resulted in similar numbers of patients in the Asian, Black, and Hispanic populations. For this reason, RENAAL provides the opportunity to evaluate renal risk factors and treatment effect on renal outcomes across these ethnic groups.

There are many published reports showing that among ethnic groups, the greatest occurrence of ESRD is observed in Black patients.[4–8] Interestingly, our findings show that Asian and Hispanic patients had similarly higher event rates for ESRD compared to Black and White patients. However, the variation in event rates accords well with the observed baseline albuminuria distribution among ethnic groups. We observed higher baseline albuminuria levels in the Asian and Hispanic patients, the same groups that experienced higher ESRD rates, while albuminuria levels and ESRD incidence rates were lower in the Black followed by White patients. This relationship between albuminuria and ESRD is consistent with our findings that higher baseline albuminuria categories are associated with higher risk for ESRD across all ethnic groups. These results support the findings of Keane *et al.*[36] and Zhang *et al.*[37] demonstrating that there is a clear association between baseline albuminuria and risk for ESRD in the overall RENAAL population.

Several risk factors, such as hypertension,[38,39] hyperglycemia,[14] and hyperlipidemia[15] appear to be associated with progression of renal disease in diabetes. However, proteinuria and hypertension are the most widely recognized risk factors for renal disease in diabetic and non-diabetic patients.[17,33,40,41] The predictive nature of proteinuria or other risk factors for renal disease in ethnic groups has not been previously examined. The current analysis demonstrates that baseline albuminuria is the strongest, independent risk predictor for ESRD in all the ethnic groups studied, regardless of the variations in baseline albuminuria level among the different populations. These findings are consistent with conclusions reported for the overall RENAAL population.[12]

Ethnic differences in response to therapy have been widely reported. However, we are not aware of data illustrating the impact of treatment on ESRD, in different ethnic populations. There is evidence indicating that the antihypertensive effects of RAS intervention with angiotensin-converting enzyme inhibitors or AIIAs as monotherapy are less pronounced compared to other therapeutic classes in Black[42–44] and Asian[44] patients. Diminished antihypertensive efficacy with RAS intervention in Hispanic and White patients has not been reported.[44]

It has been consistently reported that reduction in proteinuria with angiotensin-converting enzyme inhibition is a reliable marker for renal protection in non-diabetic patients.[16,33] Findings from the RENAAL study have demonstrated that treatment-induced changes in albuminuria are associated with renal protection in type 2 diabetic patients.[12] We therefore sought to determine whether treatment-induced changes in albuminuria existed in each

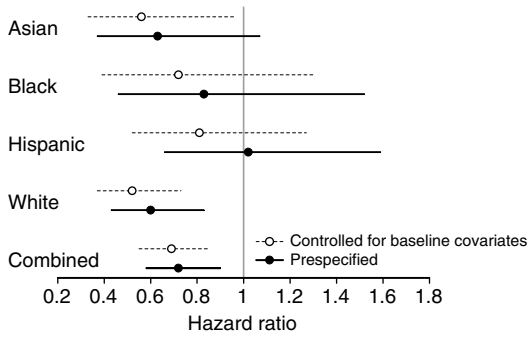


Figure 6 | ESRD treatment effect of losartan compared to placebo stratified by ethnic group. The dots and horizontal lines indicate HR point estimates and 95% CI's, respectively. The solid and dashed horizontal lines represent the analyses without (pre-specified) and with controlling for baseline covariates as summarized in Statistical analysis section, respectively. The vertical line indicates a reference HR of 1.0, or no difference between treatment groups.

Table 3 | Treatment effect of losartan on ESRD by ethnic group

Race	Losartan		Placebo		Pre-specified HR (95% CI)	Adjusted HR (95% CI)
	N	Event (rate)	*N*	Event (rate)		
Asian	117	22 (66.6)	135	37 (102)	0.63 (0.37, 1.07)	0.64 (0.37, 1.09)
Black	125	22 (59.4)	105	22 (72.0)	0.83 (0.46, 1.52)	0.93 (0.51, 1.69)
Hispanic	140	42 (111)	137	39 (108)	1.02 (0.66, 1.59)	1.14 (0.73, 1.77)
White	358	58 (54.5)	377	90 (84.1)	0.60 (0.43, 0.83)	0.62 (0.45, 0.87)

BP: blood pressure; CI: confidence interval; ESRD: end-stage renal disease; HR, hazard ratio.
All patients (except patients with other race) were included with missing covariates imputed.
Event: no. of patients with ESRD; rate: event rate per 1000 years of follow-up; pre-specified: a Cox model with treatment group and region as covariates and baseline proteinuria level ($<$ or $\geqslant$2 g/g) as strata; adjusted: a multivariate Cox model with treatment group, time-varying systolic and diastolic BP as covariates.
Pre-specified analysis and adjusted for time-varying BP.

ethnic group and whether a similar reduction in albuminuria would lead to similar renal protection among the different ethnic groups. Indeed, the current analysis shows that a progressive decline in albuminuria from baseline is observed in all ethnic groups. Interestingly, the magnitude of reduction varies among ethnic groups; however, the quantitative relationship between degree of albuminuria reduction and degree of renal protection appears to be similar across ethnic groups.

Regardless of the reported ethnic differences in response to RAS intervention, the present analysis shows that treatment with losartan affords renal protection as assessed by a reduction in ESRD in all ethnic groups. In the pre-specified analysis, a favorable treatment effect on ESRD was detected in Asian, Black, and White patients, whereas a neutral treatment effect was observed in Hispanic patients. We found that the observed differences in treatment effect among ethnic groups may be explained by treatment group imbalances in baseline albuminuria, the strongest risk predictor for all ethnic groups. Accounting for baseline imbalances (among treatment groups) in albuminuria and other independent risk factors, improved treatment effects on ESRD with losartan was observed across all ethnic groups, most notably in Hispanic patients. Not surprisingly, in all ethnic groups, baseline albuminuria had the greatest impact of all the risk factors on the improved treatment effects (data not shown).

All ethnic groups experienced decreases in diastolic BP and systolic BP with losartan (data not shown). Of note, the Asian group experienced significantly greater systolic BP reductions from baseline in the losartan versus placebo groups. For each ethnic group, we explored the effect of treated BP as a time-varying covariate on treatment effect for ESRD. The results of this analysis suggest that treated BP did not have a notable impact on treatment effect on ESRD in each ethnic group.

Certainly, factors other than biological risk parameters may have played a role in the treatment effect on ESRD. The Asian patients in the RENAAL study had the lowest rate of discontinuation from study therapy,[45] while notably higher discontinuation rates were observed across the other ethnic groups. It is plausible that study therapy compliance may have been an important factor in the degree of benefit derived from losartan treatment. We assessed the body weight-adjusted dose of losartan across ethnic groups and did not find a relationship between losartan dose (weight adjusted) and the observed differences in treatment effect on ESRD among these groups. And other factors that cannot be quantitated, such as lifestyle and medical environment differences may have played a role in the treatment effect of losartan. In the pre-defined subgroup analysis, no statistical interaction between ethnicity and treatment was detected for ESRD (data not shown).

The RENAAL study was not designed to make comparisons across ethnic groups. Therefore, the observed variations in treatment effect on ESRD and albuminuria reduction among the four ethnic groups are not unexpected. Nevertheless, the results of the present report should be interpreted with caution as evaluation of losartan's renoprotective effect by ethnic group was not the primary aim of the study.

In summary, our findings indicate, for all ethnic groups studied, the most important, independent baseline risk predictor for ESRD is albuminuria. The degree of treatment-induced albuminuria reduction is similarly associated with the degree of long-term renoprotection for all ethnic groups. Furthermore, in patients with type 2 diabetes and nephropathy we have shown that losartan confers renoprotection, in terms of long-term reduction of albuminuria and reduced risk for ESRD across ethnic groups. Since the RENAAL study was not powered to determine ethnic responses, these results underline the need for prospective trials where the primary aim is renal protection among different ethnic groups.

MATERIALS AND METHODS

Patients and study design

Results from the RENAAL study, a multinational, double-blind, randomized study comparing losartan versus placebo, each in addition to conventional antihypertensive therapy, excluding angiotensin-converting enzyme inhibitors and other AIIAs, were examined. RENAAL was performed in 250 centers across 28 countries. One thousand five hundred and thirteen diabetic patients with nephropathy were randomized, comprised of 252 Asian, 230 Black, 277 Hispanic, and 735 White patients. Ethnic group designation was based on patient self-designation during the enrollment phase. The study design, inclusion/exclusion criteria, and the treatment protocols have been reported previously.[46] Nephropathy was defined as urinary albumin:creatinine ratio >0.3 g/g in a first morning void or a 24-h urine protein >0.5 g and serum creatinine >1.5 mg/dl in males (>1.3 mg/dl in females, or males <60 kg) to 3.0 mg/dl. Patients were followed for a mean of 3.4 years. All patients signed informed consent prior to enrollment, and the study was approved by the local Institutional Review Board of each participating center.

Before randomization and every 3 months post-randomization, seated trough BP was measured, blood samples were obtained to measure chemistry and hematology parameters, and a first morning urine sample was obtained to measure the albumin:creatinine ratio. In a subset of patients, 24-h urine samples also were collected in order to measure total protein. All blood and urine tests were performed by a central laboratory.

The primary efficacy parameter was a composite end point of time to the first event of doubling of serum creatinine, ESRD, or death. ESRD was defined as the need for chronic dialysis or renal transplantation. Analyses of the components of the primary composite end point also were pre-specified. Albuminuria (proteinuria) reduction over time between two treatment groups was one of the secondary end points.

Statistical analysis

This report is based on 1494 randomized patients. Nineteen of the 1513 patients randomized belonged to 'other' ethnic groups and were excluded from the present analyses.

In the current analysis, ESRD was the end point of interest. Patients who either died or completed the study without reaching ESRD were censored at the death date or the study cutoff date of

February 10, 2001, respectively. There were no lost to follow-up patients, therefore ESRD outcomes were obtained for all randomized patients.

Albuminuria was assessed using the albumin:creatinine ratio from a first morning urine sample, and designated 'albuminuria' throughout this report. Albuminuria change at month-6 for each patient was calculated as 100 percent × (1−ratio of albuminuria at month-6 over baseline). Changes in albuminuria during the study were summarized as the mean percent change from baseline in albuminuria (on the natural log scale) by treatment groups. The 6-month time interval was selected because at this time, patients had a scheduled clinic visit, the therapy effect was considered fully present, and few renal events occurred before month-6.[12]

The cumulative proportion (%) of the ESRD end point was estimated using the Kaplan–Meier procedure. Analysis of *baseline* risk factors was performed to identify independent risk factors for ESRD. Baseline risk factors were selected among the following covariates: age (year/10), gender, weight, smoking, diastolic BP, and systolic BP, total cholesterol, serum creatinine, hemoglobin, HbA_{1C}, and albuminuria. For each ethnic group, a two-step selection procedure was used to determine independent risk predictors for ESRD: (1) a univariate analysis was performed using a Cox-regression model for selected covariates in order to identify covariates with a significance level <0.01; (2) significant covariates identified from the univariate analysis were included in a multivariate Cox-regression model, where a backward selection method was used with a significance level <0.01 to identify a covariate as an independent predictor of ESRD. The strength of a risk factor as an independent predictor included in the final analysis was determined by its magnitude of significance using χ^2 statistics.

The losartan treatment effect was determined with and without controlling for the baseline covariates as described above. Based upon the pre-specified analysis for the primary hypothesis,[29] a Cox-regression model was performed with indicators of treatment group and region as covariates, and baseline albuminuria level ($</\geqslant 2.0$ g/g) as strata. For the controlled analysis for each ethnicity, region was replaced with the significant baseline covariates (without pre-specified albuminuria ($</\geqslant 2.0$ g/g) strata) identified in the respective baseline multivariate Cox models. The HR (losartan versus placebo) with 95% CI was calculated. A similar analysis was pre-specified for the whole population where the primary outcome was controlled for significant baseline covariates, identified in a multivariate analysis.

The association between albuminuria and the ESRD end point was explored for combined treatment group, with baseline albuminuria stratified into four, *post hoc* subgroups: <0.5 g/g, $\geqslant 0.5 < 1.5$ g/g, $\geqslant 1.5 < 3.5$ g/g, and $\geqslant 3.5$ g/g with the aim of providing a smooth risk profile, when controlling for other baseline risk factors. To show a risk profile over baseline albuminuria among ethnic groups, a multivariate Cox model was used for all the patients with indicators of baseline albuminuria category by ethnic group as covariates, referencing the lowest category (<0.5 g/g) in the White group. The HR and corresponding 95% CI of each baseline albuminuria category were controlled for other baseline covariates described above (with the exception of albuminuria), using a backward selection method on the variables with alpha $= 0.01$.

To estimate the effect of albuminuria change on ESRD, an analysis similar to baseline albuminuria was performed when patients were stratified by three *post hoc* response groups in albuminuria reduction at month-6: $<0\%$, $\geqslant 0 < 30\%$ and $\geqslant 30\%$. Selection of albuminuria categories was based on such considerations as simple and clinical meaningful cut limits, adequate sample size per category, and number of patients having events per category. A cut point of 30% was selected to be consistent with the approximate overall reduction of albuminuria of 30% that was observed in this study. The lowest albuminuria reduction category ($<0\%$) in the White group was used as a common reference to compute the HR and 95% CI for each of the other ethnic groups. In addition to baseline covariates, month-6 change variables (weight, diastolic BP, systolic BP, serum creatinine, HbA_{1C}) were also included in the controlled multivariate analysis. Month-6 change for each variable was defined by the difference between month-6 and baseline values.

Some patients had missing values for relevant baseline and month-6 parameters. It is important to note, however, that no patients had missing baseline albuminuria or serum creatinine values. In order to use the intention-to-treat approach which includes all randomized patients into the multivariate Cox models, missing values either at baseline or month-6 were populated initially by imputation, using linear regression models. Each variable with missing values at baseline or month-6 was run in the model as a dependant variable with a set of baseline variables with complete measurements (independent variables), including albuminuria, serum creatinine, BP, age, gender, race, and region. The missing values were predicted from the regression model. Among 1513 randomized patients, there were few missing values (up to 3%, except 13% for HbA1c at month-6).

Although comparisons for the treatment effect on renal outcomes across ethnic groups were pre-specified subgroup analyses, the study was neither powered nor randomized to make definitive conclusions of the findings presented in this report. Most analyses presented in this report are *post hoc*.

All statistical analyses were performed using SAS version 8.

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